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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/603,936	06/26/2003	Masamichi Okada	Q75942	3419

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 04/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/603,936	OKADA ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-10* is/are rejected.

7)☒ Claim(s) *11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/26/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

This application is a divisional application of 10/031404, now US patent 6664283, filed 05/15/2002, which is a national stage entry of foreign application PCT/JP00.05074, filed on 08/01/2000. Claims 7-11 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted 6/26/2003 is acknowledged wherein claims 1-6 have been cancelled and new claims 7-11 introduced.

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating neuropathic pain comprising systemic administration of certain small molecule therapeutics identified in the specification or cited in references, does not reasonably provide enablement for any compounds which could be described by the phrase "compound having mGluR1 antagonistic activity and having no activity on groups II or III of metabolic glutamate". This is a purely functional distinction or functional language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to reliably determine the scope of the molecules claimed, absent undue experimentation.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The invention deals with a therapeutic method for treating neuropathic pain by systemically administering an appropriate mGluR1 antagonist. The method by which the compound is to be administered is expected to be similar for most compounds likely to be used to practice the invention, although certain functional groups, such as phosphate groups or oligonucleotides, which are not excluded from a broad reading of the claim, may not be suitable for certain methods of administration, such as oral administration.

The state of the prior art: It has been established in the prior art that various compounds exist which are capable of antagonizing the normal functioning of metabotropic glutamate receptors. Compounds are known which selectively antagonize certain subtypes of these receptors, and administration of such compounds is known to modify both nociceptive and neuropathic pain in experimental models of pain. These therapeutics include both small molecules and antibodies.

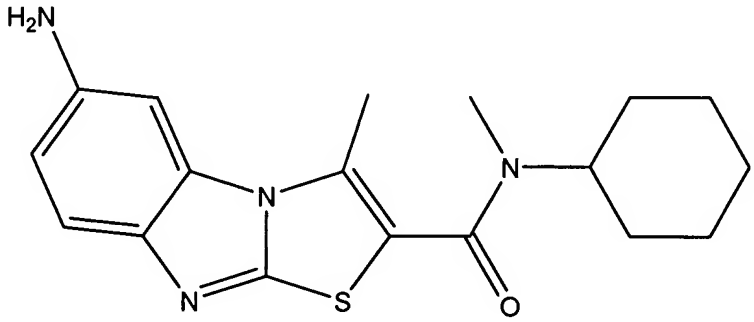
The relative skill of those in the art: The level of skill in the art is high, with a typical practitioner holding a Ph. D. or equivalent advanced degree in a an appropriate field.

The predictability or unpredictability of the art: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Because systemic administration of the appropriate compound is an essential part of the claimed invention, and because the Applicant specifically points to this aspect of the invention as differentiating it from the prior art, it is important to note that systemic administration of a drug is affected by additional factors besides the activity of the drug against its molecular target in vitro. In particular, the claimed invention requires the compound to be biostable and bioavailable when administered at a single point of entry into the body, and to be able to cross the blood-brain barrier to reach the thalamus. These critical pharmacological properties cannot be predicted from the suggested in vitro binding assay and a significant number of compounds which display excellent activity in the assay are expected to be poor drug candidates for this reason. This is especially true if, as suggested in the specification (p. 10, lines 20-22), polypeptides are used for this mode of treatment.

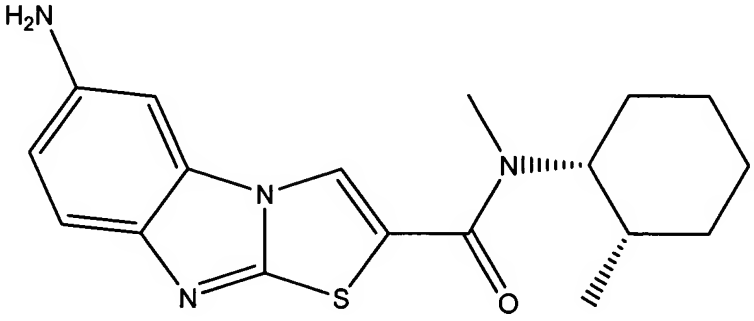
The breadth of the claims: Claim 7 identifies the invention as a method of treatment involving any possible compound which happens to possess selective antagonism for the mGluR1 metabotropic glutamate receptor. The specification further clarifies that the invention is to include both peptide and non-peptide compounds. Although polynucleotides are not explicitly mentioned, they would fall within the limits of this claim language. The claims are so broad as to include any molecule, anywhere, known in the past, present, or future to possess the property of selective mGluR1 antagonism.

The amount of direction or guidance presented: The specification includes a description of an in vitro assay which may be used to identify compounds having mGluR1 antagonism. They also describe in vivo experiments with two experimental models of neuropathic pain. The molecular target of the invention is described as well. One skilled in the art wishing to practice the invention with a compound other than those explicitly disclosed would, based on the specification, be able to design a program of drug discovery to identify novel compounds which would be useful in the claimed therapeutic method.

The presence or absence of working examples: Two examples are disclosed in the specification, and listed below:



6-amino-n-cyclohexyl-n,3-dimethylthiazolo[3,2-a]benzoimidazole-2-carboxamide



(+)-(1R,2S)-6-amino-n-methyl-N-(2-methylcyclohexyl)thiazolo[3,2-a]benzoimidazole-2-carboxamide

These compounds differ only in the placement of a single methyl group and are not representative of the broad range of compounds which the Applicant claims may be used in the

invention. Compounds whose suitability for the method cannot be judged based on the examples include, for example: nonaromatic compounds, free carboxylic acids, spiro compounds, sulfonates, pyridines, polypeptides, polynucleotides, and antibodies, all of which could include compounds possessing selective mGluR1 antagonism. Relative to the extremely broad scope of the claims, these examples serve as nothing more than a proof-of-concept for the *in vitro* and *in vivo* methods described in the specification.

The quantity of experimentation necessary: According to the Chemical Abstracts Service 2006 catalog, the Chemical Abstracts Registry contains entries for approximately 26 million organic and inorganic substances, all of which are potentially involved in the claimed method if they happen to possess selective mGluR1 antagonism. The Sigma-Aldrich Rare Chemical Library contains over 80000 compounds, all of which are commercially available and also potential candidates for use in the claimed invention. The total number of compounds known either (a) to be selective mGluR1 antagonists or (b) to not be selective mGluR1 antagonists is merely an insignificant fraction of the total number of compounds whose mGluR1 antagonizing activity is not known. While the existing literature on the mGluR1 receptor and its antagonists does suggest certain classes of molecules known to possess the desired properties, it does not provide any basis on which to believe that those classes of compounds currently known exhaust the entire range of molecules which are defined by the claim language, "a compound having mGlulR1 antagonistic activity and having no activity on Group II and Group III of metabotropic glutamate". One skilled in the art wishing to practice the invention with the full range of selective mGluR1 antagonists beyond the meager number disclosed in the specification would, in addition to carrying out *in vitro* studies on the molecular target, also be required to undertake *in*

vivo tests in an animal model of neuropathic pain such as the ones disclosed in the specification. Animal experiments include, along with the actual surgery, administration of the potential pharmaceutical compound, and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, especially if said molecule is a polypeptide, these animal experiments would need to be repeated thousands of times, and involve the maintenance, killing, and disposal of tens of thousands of experimental animals, to establish the suitability or lack thereof for each compound found to possess mGluR1 antagonism *in vitro*. This sort of industrial-scale drug discovery program would present an undue amount of experimentation to anyone wishing to practice the invention.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, especially the unpredictability of the art, the broad scope of the claim, the paucity of working examples, and the excessive amount of necessary experimentation, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of neuropathic pain using each and every "compound having mGlulR1 antagonistic activity and having no activity on Group II and Group III of metabotropic glutamate".

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Fisher et. al. (PTO-1449 submitted by Applicant). These references teach a method whereby a rat suffering from an experimentally induced nerve constriction injury was treated for neuropathic pain by the intrathecal administration of antagonists specific to the group I metabotropic glutamate receptors. (Figures 1-3, pp. 62-64)

It is generally known within the field of pharmacology that systemic administration of a drug, if possible, is preferred to intrathecal administration for reasons of convenience and patient comfort. A therapeutic regime for use in humans is an essentially different undertaking from an experimental model in rats. While intrathecal administration may be ideal for the initial characterization of a compound in the laboratory, a practitioner of ordinary skill would not therefore assume that the authors of these references intended their compounds to be administered intrathecally in all circumstances, but rather would have intended their compounds for systemic administration.

Therefore the claimed inventions of claims 7-8 are anticipated by Fisher et. al.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fundytus et. al. and Fisher et. al. (PTO-1449 submitted by Applicant). These references teach a method whereby a rat suffering from an experimentally induced nerve constriction injury was treated for neuropathic pain by the intrathecal administration of antagonists specific to the group I metabotropic glutamate receptors. (Fisher et. al. – Figures 1-3, pp. 62-64, Fundytus et. al. – Figure 3, p. 734) They do not teach the oral administration of such compounds.

It is generally known within the field of pharmacology that systemic administration of a drug, if possible, is preferred to intrathecal administration for reasons of convenience and patient comfort. A therapeutic regime for use in humans is an essentially different undertaking from an experimental model in rats. While intrathecal administration may be ideal for the initial characterization of a compound in the laboratory, a practitioner of ordinary skill would not therefore assume that the authors of these references intended their compounds to be administered intrathecally in all circumstances.

When administering a compound to humans, it is desirable that administration be accomplished by a simple, painless procedure which can be carried out by the patient him or herself without the direct supervision of a physician or other professional, a concern which is irrelevant when the patient is a rat being used in a nerve ligation model of neuropathic pain. An orally administered, systemically distributed compound fits such a requirement more effectively than a topical intrathecally administered compound. Therefore, when translating their initial *in vivo* findings into a clinically effective therapy, the aforementioned researchers would be motivated to administer their compounds systemically by oral administration in order to provide the least invasive route of administration possible. One would have reasonably expected success in light of the vast number of pharmaceutical compositions which are currently orally administered. Therefore the invention taken as a whole is *prima facie* obvious.

Claim Objections

Claim 11 is objected to as depending from a rejected base claim but would be acceptable if rewritten in independent form, including all the limitations of the base claim. Claim 11 is found to be free of the prior art and fully enabled by the specification.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday through Friday, 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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